CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

74446

CHEMISTRY REVIEW(S)

1 CHEMISTRY REVIEW NO. 7

2. ANDA # 74-446

3. NAME AND ADDRESS OF APPLICANT

Novopharm Ltd.
Toronto, Canada

4. LEGAL BASIS FOR ANDA SUBMISSIONS: (see review #1)

5. SUPPLEMENT(s) N/A

6. PROPRIETARY NAME 7. NONPROPRIETARY NAME

N/A Terazosin Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9/. AMENDMENTS AND OTHER DATES

DOA 12/16/93; Tel Com 1/7/94; NC 1/7/94; Letter 2/3/94; NC 2/14/94; NC 3/14/94; NA 6/22/94; NC 6/28/94; NC 8/10/94; Amend 12/21/94; NA 6/30/95; Amend (minor) 9/28/95; Tel Memo 10/20/95; Amend 11/2/95; Amend 12/19/96; NC 2/2/96 & 2/2/96; Minor Amend 2/29/96; Label review 3/11/96; NC 8/7/96; NC 8/16/96; NC 10/23/96; NC 9/13/96; Amend 10/30/96; Label Rev 11/12/96; Amend 11/7/96; Label Review 11/13/96; Method validation package from DDA-STL (HFD-920) (Methods OK) 3/12/96; Tentative Approval Letter (TAPL) 11/26/96; NC 1/8/97; NC 2/24/97; NC 9/28/98; Amend 1/29/99; Amend 2/10/99/; Bio comments to applicant 8/4/99; FAX deficiencies 8/6/99; NC 8/9/99; FAX amendment 9/3/99; T. Approval Letter 12/29/99; Amend (Minor) 3/17/00*; Telecom 4/17/00.

* Amendment reviewed.

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC

Hypertension Rx

12. RELATED IND/NDA/DMF(s)

See review #1

13. DOSAGE FORM 14. POTENCY

Tablets: Oval shaped flat-faced beveled tablets.

Color Engraved

White	N842 one side 1 opposite	1 mg
Dark orange	N843 one side 2 opposite	2 mg
Brown	N844 one side 5 opposite	5 mg
Dark Green	N847 one side 10 opposite	10 mg

15. CHEMICAL NAME AND STRUCTURE

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolin-4-[(tetrahydro-2-furanyl)carbonyl]-,monohydrochloride, MW = 423.89. Molecular formula $C_{19}H_{25}N_5O_4 \bullet HCl$
See review #1.

16. RECORDS AND REPORTS N/A

17. COMMENTS

Novopharm's amendment of 4/17/00 withdrew Paragraph IV Certification that was filed for US Patent No. 5,212,176 and US Patent No. 5,294,615, due to the fact that they are late listing patients. They also certified that there was no further changes made to their ANDA since they received our Tentative Approval Letter of December 29, 1999.

Bio found the in-vivo (5 mg tablet) and in-vitro studies (1 mg, 2 mg and 10 mg tablets) from batches made from (DMF were Bioequivalent to Abbott's Hytrin Tablets on 6/5/94.

New in-vitro bio studies were conducted on four batches (1 mg, 2 mg, 5 mg, and 10 mg tablets) made with drug substance (DMF- The Division of Bioequivalence has evaluate the dissolution profile studies on 8/4/99, and found them acceptable, and Bioequivalent to Abbott's Hytrin Tablets on 6/5/94.

Labeling was acceptable per 11/26/96 TAPL.

EER found acceptable on 5/3/00.

CDER's St. Louis Lab., satisfactorily validated all analytical methods used to analyze the drug substance and drug product on 3/7/96.

18. CONCLUSIONS AND RECOMMENDATIONS

Approve ANDA 74-446.

19. REVIEWER:	DATE COMPLETED:
Stephen Sherken	5/2/00

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pages of trade

secret and/or

confidential

commercial

information

Chem Review #7

ANDA Number: 74-446

FIRM: Novopharm Ltd. DOSAGE FORM: Terazosin Tablets

STRENGTHS: 1 mg, 2 mg, 5 mg, and 10 mg.

CGMP STATEMENT/EER UPDATE STATEMENT: EER acceptable 5/3/00.

BIO STUDY: Found satisfactory on June 5, 1994, and August 4, 1999.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

Methods were validated on March 12, 1996. The methods were satisfactory.

STABILITY - ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION

Three month stability data at 40°C/75% RH was found satisfactory for the 1, 2, 5 and 10 mg tablets in bottles of 100 tablets, bottles of 1000 tablets and unit dose packages of 100 tablets. The containers that were described in the stability studies are the same containers that are described in the container section.

LABELING:

Labels and labeling were found satisfactory on 3/11/96.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.)

Batch manufactured with drug substance.

5 mg tablets. Lot PD-2504.

DMF found adequate on 5/1/00. batch 920507 passed all required tests and specifications.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED BY THE SAME PROCESS?)

Batches manufactured with drug substance. batch 920507 passed all required tests and specifications.

1 mg tablets. Lot PD-2502. Novopharm used the same process that was used to manufacture the bio batch.

2 mg tablets. Lot PD-2503. Novopharm used the same

10 tablets. Lot PD-2505. Novopharm used the same process that as was used to manufacture the bio batch.

Batches manufactured with drug substances.

DMF found adequate on 9/1/99. batch 33703 passed all required tests and specifications.

1 mg tablets. Lot PD-3184. Novopharm used the same process that was used to manufacture the bio batch.

2 mg tablets. Lot PD-3185. Novopharm used the same process that was used to manufacture the bio batch.

5 mg tablets. Lot PD-3186. Novopharm used the same process that was used to manufacture the bio batch.

10 tablets. Lot PD-3187. Novopharm used the same process that as was used to manufacture the bio batch.

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

1 mg Terazosin Tablets. 6x scaleup.

2 mg Terazosin Tablets. 10x scaleup.

5 mg Terazosin Tablets. 10x scaleup.

10 mg Tablets. 4x scaleup.

Except for the differences in the sizes of the blenders, all strengths of Terazosin Tablets will be manufactured by the same method that was used to manufacture the bio and 7 stability batches.

cc: ANDA 74-446
HFD-625/SSherken/5/2/00
HFD-623/Gill/5/2/00

/S/ 5/2/00

/S/ 5-2-00

ANDA Number: 74-446

FIRM: Novopharm Ltd. DOSAGE FORM: Terazosin Tablets

STRENGTHS: 1 mg, 2 mg, 5 mg, and 10 mg.

CGMP STATEMENT/EER UPDATE STATEMENT: EER acceptable on 8/9/99.

BIO STUDY: Found acceptable on June 5, 1994, and August 4, 1999.

METHODS VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM)

Methods were satisfactorily validated on March 7, 1996.

STABILITY - ARE THE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION

Three month stability at 40°C/75% RH were found satisfactory for the 1, 2, 5 and 10 mg tablets manufactured with ICFI's and Uetikon's drug substances, in bottles of 100 tablets with pressure seal and heat seal liners, bottles of 1000 tablets with pressure seal liners, and unit dose packages of 100 tablets. The containers used in the stability studies are the same as described in the container sections.

LABELING:

Labels and labeling were found satisfactory on 3/11/96.

STERILIZATION VALIDATION (IF APPLICABLE):

N/A

SIZE OF BIO BATCH - (FIRM'S SOURCE OF NDS O.K.)

tablet size batch of Kg. (5 mg) for lot 2504 PD.

DMF was found adequate on 7/28/99.

manufactures the drug substance as the principal supplier for Novopharm.

batch 920507 was used to manufacture the bio and three stability batches. It passed all required tests and specifications.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED BY THE SAME PROCESS?)

Batches manufactured with drug substance.

-tablet size batch (1 mg) Kg) lot 2502 PD - Same process as was used to manufacture the bio batch.

tablet size batch (2 mg) Kg) lot 2503 PD - Same process as was used to manufacture the bio batch.

-tablet size batch (10 mg) Kg) lot 2505 PD - Same process as was used to manufacture the bio batch.

Batches manufactured with drug substance.

tablet size batch (1 mg) Kg) lot 3184 PD - Same process as was used to manufacture the bio batch.

tablet size batch (2 mg) Kg) lot 3185 PD - Same process as was used to manufacture the bio batch.

-tablet size batch (5 mg) Kg) lot 3186 PD - Same process was used to manufacture the bio batch.

-tablet size batch (10 mg) Kg) lot 3187 PD - Same process as was used to manufacture the bio batch.

DMF was found adequate on 9/14/99.

manufactures the drug substance as an alternative supplier for Novopharm.

batch 33703 was used to manufacture the four stability batches. It passed all required tests and specifications.

PROPOSED PRODUCTION BATCHES - MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?

1 mg Terazosin Tablets: Production size = tablets. Approximately a 6x scaleup from the executed stability batches.

2 mg Terazosin Tablets: Production size = tablets. Approximately a 10x scaleup from the executed stability batches.

5 mg Terazosin Tablets: Production size = tablets. Approximately a 10x scaleup from the executed bio and stability batch.

10 mg Terazosin Tablets: Production size = tablets. Approximately a 4x scaleup from the executed stability batches.

Except for the differences in the sizes of the blenders, all strengths of Terazosin Tablets will be manufactured by the same methods that were used to manufacture the one bio and seven executed stability batches.

/S/ 9/14/99

Prepared by Stephen Sherken on September 14, 1999.

DSG II
9-21-99

38. Chemistry Comments to be provided to the Applicant

ANDA: 74-446 APPLICANT: Novopharm Limited

DRUG PRODUCT: Terazosin Tablets, 1 mg, 2 mg, 5mg and 10 mg.

The deficiencies presented below represent FACSIMILE deficiencies.

A. Deficiencies:

1. Please submit blend uniformity data for lots 3184PD, 3185PD, 3186PD and 3187PD. Please revise your specifications for blend uniformity to 90.0% to 110.0% for the mean and a relative standard deviation of NMT % with a sample size of not more than 1 to 3 dosage units.

2. Please show that amber 13.5 mil film passes all required tests found in USP's section <661> for

3. Please test the newly proposed blister pack combination for container permeation in USP section <671> for Single Unit Containers and Unit Dose Containers for Capsules and Tablets.

4. Please revise the four stability reports that were used to report the accelerated stability data from the four batches of tablets that were packaged in 100s, 60 cc HDPE bottles and 33 mm heat-seal liners. These reports should include the correct liners that were used to seal the tablets into the 60 cc HDPE bottles. If, however, the four stability reports correctly identify the liner as a non-heat seal liner, then you must provide 3 months accelerated stability data in 60 cc HDPE bottles with 33 mm heat-seal liners and caps. In addition, please confirm if the 60 cc, 500 cc, and 625 cc HDPE bottles that were put on accelerated stability were manufactured with resin or resin.

5. Please justify why the 1 mg tablet was tested for dissolution in mL of water, rather than in 900 mL of water, as required by the Division of Bioequivalence.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please acknowledge that a satisfactory compliance evaluation for the firms referenced in the application is required prior to approval of the application. We have requested an evaluation of each firm from the Office of Compliance.

2. Your Bioequivalence information and request for a waiver is pending review.

Sincerely yours,

/S/

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I/II
Office of Generic Drugs
Center for Drug Evaluation and Research